

# Educational Items Section

## Short Communication

## Genetics and Public Health

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### I - Introduction

The role of public health is to ensure that the basic conditions required for people to be healthy are present. Until recently, public health focused mostly on environmental causes and risk factors for disease, such as infections, cigarette smoking, diet, etc. Since the sequencing of the human genome has been completed, high hopes rest on the potential to prevent the impact of genetic risk factors or susceptibilities to disease.

Advances in genetic knowledge and technology could be used to try to prevent disease and improve population health.

The perceived role of genetics in public health is changing, as is the definition of what is a genetic disease. The role of genetics in public health is broadened if we consider all the diseases for which genetics might play a role, either by the presence of a genetic susceptibility for the development of this disease or for response to treatment, or by the presence

of protective genetic factors, such as in resistance to infection.

One day, it might be possible to determine for each individual which genetic susceptibilities and protective factors each individual possesses, and act accordingly to prevent the occurrence of disease. In the meantime, the role of genetics in public health is mostly limited to monogenic diseases.

## ***II - Populations targeted by public health genetics interventions***

Public health considers the overall health of the population as a group, and not the health of each individual. Since resources for public health interventions are limited, priorities need to be established to determine which interventions will be most beneficial to the population as a whole. These priorities will be based on the characteristics of the disease, such as its prevalence, its severity, and treatment availability, as well as the amount of resources needed for the intervention.

Monogenic diseases are rare. Is it justifiable to implement population-based interventions to identify a few rare cases of a particular genetic disease? There is no single right answer to this question. It depends on the burden these rare cases represent for society, on our ability to act to attenuate this burden, and on the value we place on obtaining an early diagnosis, compared to the complexity of detecting these cases and the amount of resources needed to detect them. For example, newborn screening for phenylketonuria is considered beneficial because it makes it possible for the children identified through screening, who would otherwise have developed severe mental retardation, to develop normally by following a special diet. In the majority of developed countries, all newborns are screened for phenylketonuria to detect a handful of cases, because the impact of treatment on these children's potential ability to contribute to society is so great. On the other hand, similar newborn screening for Huntington disease is not being considered, because it is a late-onset disease for which there is no treatment and no clear benefit to an early diagnosis. Screening would not change the impact of the disease on the affected individuals or its burden on society.

To improve the yield of a screening program for a genetic disease, one option is to target a population at higher risk of disease, often the families of affected cases. This approach limits the amount of resources needed for screening and increases the yield of screening. It unfortunately is limited by the fact that many new cases of genetic disease occur in individuals with no family history who would not be identified by family-based screening. In some cases, ethnic groups can be the target population of screening programs, when prevalence of the disease in question is particularly high in that ethnic group. For example, Ashkenaze Jewish populations are screened for Tay-

Sachs disease. In programs targeted at specific communities, it is important to ensure that the community is in favor of screening and that it does not become a source of stigmatization for the community.

## ***III - Ethical, legal, and social implications of public health genetic interventions***

### ***III - 1. Use of genetic information: confidentiality and discrimination***

The issue of confidentiality of genetic information is frequently raised. Genetic information is different from other types of personal information found in a medical chart. First, genetic information does not change over time: the presence of a mutation or a polymorphism in an individual is immutable. Second, genetic information about one individual has implications not only for the individual in question, but also for his/her family members, since the genetic abnormalities are heritable in most cases. In some cases, genetic information is used to confirm a clinical diagnosis, but it is increasingly used to confer a level of risk or susceptibility for the development a specific condition. In that context, it is not surprising that some are worried that information about a specific genetic susceptibility might be used by insurers or employers as a source of discrimination.

### ***III - 2. DNA banks***

Genetic research often requires the collection of DNA samples. Many DNA banks were formed from DNA samples collected for specific research projects or from blood samples collected for newborn screening. Once they have served their intended use, what should now be done with these samples? Who do they belong to? Can the researcher use them for other purposes without the consent of those who gave these samples? Can he only do it if he anonymizes the samples first? Or does the researcher need to contact each individual to renew his/her consent? To respect the autonomy of individuals who participated in previous research projects, it would be necessary to contact them again to obtain renewed consent before using their samples for other research projects. On the other hand, these samples are easily accessible and could be used to further scientific knowledge for the benefit of society without major negative impact on the individual who provided the sample, especially if the samples are anonymized. In some cases, the nature of the prospective research will also influence the decision to use or not use samples from a DNA bank. Researchers and ethicists all over the world are faced with these issues. Institutional review boards are assessing each research project based on its specific context, because no consensus has been reached for now on procedures for the use of DNA banks in research.

### ***III - 3. Prenatal diagnosis, assisted reproduction and embryo selection***

Assisted reproduction has made it necessary to redefine fundamental concepts, such as paternity and maternity. We now use the terms biological mother, gestational mother (or surrogate mother), and social mother. We also differentiate between biological father and social father. Before DNA tests, paternity was always assumed, but it is now possible to determine with strong certainty whether an individual is or isn't a given child's biological father. In the past, maternity was simply attributed to the woman who had given birth to the child. But these days, it is possible for a woman to have an embryo conceived with her own eggs carried to term by another woman. The first woman is then the biological mother, and the second the gestational mother. The social mother will be the one acting as a parent to the child in question.

Assisted reproduction is not reserved for infertile couples anymore, but is also used by couple who want to ensure that their child will be born without a specific hereditary disease, or even to make sure that their child will be a matched donor for an older sibling in need of a bone marrow transplant. Genetic tests performed on embryos make it possible to select only embryos that fit certain criteria. For now, this technology is mostly used to avoid the birth of children with severe hereditary childhood diseases, but it is feared that it opens the door to embryo selection based on other criteria, such as physical appearance or intellectual ability.

When a pregnant woman is offered the possibility of undergoing prenatal diagnosis for genetic diseases through amniocentesis or chorionic villous sampling, it implies that selective abortion is an option they will consider if the fetus is indeed affected with a genetic disease. For some, this option is unacceptable for ethical, moral, and/or religious reasons. It raises the question of the legal status of the embryo, the definition of human life and of a human being.

#### **IV - Examples of the role of public health in genetics**

There are already many examples of the role of public health in genetics. Better known examples deal with reproductive technologies (prenatal screening, carrier screening) and newborn screening. More recent examples in the adult setting concern genetic susceptibility screening and pharmacogenetics.

##### **IV - 1. Folic acid and neural tube defects**

Neural tube defects (NTD) account for an important part of birth defect-related infantile mortality and morbidity. Their incidence tends to be decreasing over time (secular trend). During the 1980s, studies have shown a decrease in the recurrence of NTD in subsequent pregnancies with the use of folic acid for women having already had a child with a NTD. Since then, studies done in women with no family history of NTD have also shown lower incidence rates of children born with NTD in women who took folic acid

supplements. Even though the way in which folic acid acts to prevent NTD has not been elucidated, these observed findings have led to the hypothesis that folic acid supplementation would be beneficial to all women planning a pregnancy, to prevent the birth of a child with a NTD.

Because the neural tube closes during the fourth week of gestation, it is recommended to start folic acid supplementation before conception. The minimal dose needed to obtain an effect has not been established, but the usually recommended daily dose is 400 micrograms in women with no specific risk factor, and should be started at least 3 months before conception. However, supplementation often does not occur, either because women are not aware of the benefits of folic acid supplementation or because pregnancy was not planned.

To address this problem, some countries have decided to add folic acid to the food supply, most often in flour. This type of public health intervention has occurred in the past to prevent other diseases: iodized salt to prevent goiter, and vitamin D in milk to prevent rickets. Folic acid fortification of flour has not been done without controversy. Some fear that folic acid fortification will mask vitamin B12 deficiency and delay its diagnosis. Others worry about long-term effects of a folic acid-fortified diet or about potential interactions between folic acid and prescribed drugs. No study has shown that this fortification strategy would be sufficient to reduce the incidence of NTD in the population. In spite of all that, many professional organizations have declared themselves in favor of fortification. Folic acid fortification has been established at the end of the 1990s in many developed countries, most often in flour. Studies done since fortification seem to show a significant reduction in the incidence of NTD in the population, even when accounting for the secular trend.

##### **IV - 2. Newborn screening**

Phenylketonuria (PKU) is the first example of population-based genetic screening. It was put in place in the U.S.A. in the early 1960s, thanks to the development by Dr Robert Guthrie of a technique allowing the measurement of blood phenylalanine levels using blood samples collected on filter paper. Samples collected in this way are easy to store and ship, and can be preserved for extended periods of time. The technique itself is cheap and easy to perform. These characteristics have made it possible to develop large-scale screening programs. Newborn screening for PKU is now performed by the state in most developed countries.

In the wake of newborn screening tests, a screening "system" was developed. Today, a newborn screening system includes sample collection and shipment to screening facilities, performance of the screening test in the laboratory, diffusion of test results to parents and

referring physicians, and, for newborns with abnormal results, rapid access to specialized evaluation and appropriate care. In parallel, severe quality control criteria have been established and voluntary laboratory quality control programs are managed by government agencies, such as the Center for Disease Control in the U.S.A.

Since the 1960s, other diseases have been added to newborn screening panels. The list varies by region, but it almost always includes congenital hypothyroidism, and often includes galactosemia, tyrosinemia, sickle cell anemia, and/or congenital adrenal hyperplasia. For all these diseases, a dietary-based or drug-based treatment is available to prevent the effects of the disease or attempt to control their progression, and it seems preferable to start these treatments as early as possible.

In the last few years, a new technology, tandem mass spectrometry (MS/MS), makes it possible to detect over 30 metabolic diseases during the newborn period, such as aminoacidemias, organic acidurias, and urea cycle defects, to name a few. The use of this technology for newborn screening is controversial for several reasons. Among the diseases that can be detected with MS/MS, some have a poorly defined natural history. In those cases, it is difficult to predict what will happen to the affected newborn and the impact that early diagnosis and treatment could have. It is not clear whether dietary treatment will be as effective in all cases. However, newborn screening using MS/MS would make it possible to learn more about these diseases, which might otherwise go undetected (even if symptomatic). In the U.S.A., advocacy groups formed by parents of children with diseases detectable with MS/MS are lobbying for the addition of this technology to state-run newborn screening programs. Those opposed to using MS/MS for newborn screening argue that there is no evidence that early diagnosis and treatment of these diseases will improve their natural course, which goes against the criteria largely used to decide whether or not to add new diseases to newborn screening programs. They stress that the availability of the technology and its capacity to detect disease does not mean that the information it provides is valuable for newborns.

Newborn screening for cystic fibrosis is also currently debated. Newborn screening programs for cystic fibrosis already exist in many regions of the world: in Wisconsin and Colorado (USA), in Brittany (France), and some regions of the United Kingdom and Australia. Some studies have shown that children identified through newborn screening achieve better nutritional status and/or better respiratory function than those diagnosed through symptoms, but these differences are mild and tend to disappear over time. The main newborn screening criteria, as defined by the World Health Organization, state that an effective treatment must be available and that the early

application of that treatment must improve the health outcome of the child. Even though long term impact of early diagnosis of cystic fibrosis on the evolution of disease has not been irrevocably established, some argue that early diagnosis is of benefit to parents because it avoids unnecessary anxiety related to delayed diagnosis in a symptomatic child, and enables them to make informed reproductive decisions for future pregnancies. The benefit is not for the child itself, but for parents, and it is not related to the early onset of effective treatment. According to this argument, it would be justifiable to screen for genetic conditions with no known effective treatment but whose early diagnosis would be of value to the parents. In the case of cystic fibrosis, early diagnosis can possibly be of value to the child, but this would not be the case for other diseases for which newborn screening has been advocated, such as Duchenne muscular dystrophy and Fragile X syndrome.

#### **IV - 3. Carrier screening in the context of reproductive decisions**

The first carrier-screening program for recessive diseases was developed in the Ashkenazi Jewish communities in New York and Washington, D.C., in the U.S.A. With the support of the community and religious officials, a carrier-screening program for Tay-Sachs disease was established in the early 1970s, shortly after the discovery of the enzyme whose deficiency is the cause of the disease. Tay-Sachs disease then had a relatively high prevalence in the Ashkenazi Jewish community. This disease causes progressive neurodegeneration starting in the first year of life and inevitably leading to the child's death, usually by four years of age. Both the community members and the health professionals involved agreed that this disease is so severe that it would be preferable to take measures to avoid the birth of affected children. The screening strategy has been adapted to the needs and realities of the different communities: in orthodox communities where selective abortion was not acceptable, premarital screening is performed and results are taken into account in the rabbi's decision to bless the marriage or not, which has been deemed acceptable by the community. Carrier screening programs for Tay-Sachs disease now exist in Ashkenazi Jewish communities around the world. Thanks to these programs, the incidence of the disease has decreased by over 90% in these communities. In the wake of this success, other diseases with relatively high prevalence in Ashkenazi Jewish communities have been added to carrier screening panels, such as Canavan disease and Gaucher disease, to name a few.

In response to the success of Tay-Sachs carrier screening in Ashkenazi Jewish communities, similar programs have been developed in other communities where an autosomal recessive disease was highly prevalent in children, such as carrier screening for beta-

thalassemia in Cyprus and Sardinia. These programs have also led to drastic reductions in disease prevalence in these communities. Carrier screening programs for sickle cell anemia in African Americans in the U.S.A. in the 1970s have not had the same success, partly because the distinction between being a healthy carrier and having the disease was not made clear. This had led to discrimination against carriers.

Recently, the American College of Obstetrics and Gynecology has recommended that all pregnant women be offered carrier screening for cystic fibrosis. This recommendation has been questioned by some, because screening is routinely offered when pregnancy is already ongoing and because cystic fibrosis is not considered as severe as Tay-Sachs disease.

#### **IV - 4. Prenatal screening for aneuploidy and neural tube defects**

For a detailed discussion of what is available in prenatal diagnosis, see "Prenatal Diagnosis" section.

In terms of population health, it is of note that prenatal screening for chromosomal abnormalities and neural tube defects is offered to pregnant women in many countries. These screening programs may be targeted at women with specific risk factors (i.e. according to maternal age), or to all pregnant women. In most cases, newborns with chromosomal abnormalities or neural tube defect are born of mothers with no specific risk factors. A screening test done during pregnancy can identify those women at higher risk of carrying a fetus with one of these conditions. This blood test, which measures a combination of serum and/or ultrasound markers, is not a diagnostic test: like all screening tests, it tends to be highly sensitive, but not necessarily very specific. The role of a screening test is to detect all cases of the targeted condition, at the expense of a certain amount of false positive results. For prenatal screening, the test result is usually given as the probability that the fetus is affected, and the result is considered "positive" when this probability is higher than a specific threshold, usually between 1/400 and 1/200. Since this threshold is relatively low, there is inevitably a high proportion of false positive results, i.e. pregnancies with test results above the threshold and considered at high risk of having an affected fetus, but whose fetus is actually not affected. In a screening context, we tolerate a certain amount of false positive results that will have to undergo definitive diagnostic testing through amniocentesis and incur the associated risk of miscarriage. It is the price to pay to reduce as much as possible the rate of false negative results, i.e. a result placing the risk below the threshold when the fetus is actually affected. These screening programs have been developed to give women the possibility of terminating the pregnancy if the fetus is found to be affected. In general, this option is considered acceptable because most people consider these conditions to be severe enough and prevalent enough to

justify a population-based screening program. Those who consider termination to be unacceptable can select out of the screening process.

#### **IV - 5. Screening for genetic susceptibilities in adults**

Since the sequencing of the human genome, advances in genetic knowledge has led us to consider the potential use of genetic information to assess individual susceptibility to disease. Although this is not widely possible yet, there are some examples of the use of genetic tests for that purpose. These examples raise questions about the real clinical utility of that type of information at the individual level.

Hereditary hemochromatosis is an autosomal recessive disease. Individuals who suffer from this disease can develop cirrhosis of the liver, diabetes, and cardiomyopathy. Symptoms are caused by a defect in iron metabolism, which leads to iron deposition in tissues. Two main mutations in the hemochromatosis gene have been identified, C282Y and H63D. Most cases are C282Y homozygotes. Regular phlebotomies reduce iron deposition and can help prevent or reduce symptoms. For that reason, hemochromatosis is considered an ideal target for population-based screening. The use of a genetic test as a screening test for hereditary hemochromatosis is justified if we assume that penetrance of the disease is high, i.e. that most C282Y homozygotes will develop symptoms of hemochromatosis in their lifetime if untreated, and that they would benefit from early diagnosis and preventive treatment. Unfortunately, penetrance seems lower than previously thought: it seems that only a minority of C282Y homozygotes actually develop symptoms of hemochromatosis in their lifetime. The value of population-based genetic screening for hemochromatosis is being questioned. It is currently recommended to use transferrin saturation level as a screening test for hemochromatosis. This is a biochemical index of iron overload, and is closer to the phenotype of hemochromatosis than the genetic test.

Factor V Leiden (FVL) is a variant of factor V, a coagulation factor. This variant is associated with an increased risk of thrombosis. Even though the presence of FVL in an individual with a history of thrombosis can help explain the cause of the thrombosis, it does not usually change immediate treatment or long-term management of that individual, who will be treated as any other individual with a personal history of thrombosis. On the other hand, not all individuals who have FVL will develop thrombosis. It is difficult to justify population-based screening for FVL, and especially to submit them to long-term prophylactic anticoagulation treatment, which is associated with significant risks of bleeding. Other factors also influence the risk of thrombosis in these individuals, such as smoking and hormonal therapy, and make it difficult to predict risk of thrombosis on an individual basis.

As our knowledge of gene-environment interactions increases, it might be possible to improve our assessment of individual disease susceptibility by using predictive models based on combinations of genetic and environmental risk factors. For now, the impact of genetic susceptibility is difficult to assess, especially on an individual basis.

#### **IV - 6. Pharmacogenetics and ecogenetics**

Pharmacogenetics is a field of genetics focusing on the role of genetics in individual variability of drug response and side effect occurrence. If we can predict the pharmacologic response of a given individual to a specific drug based on the presence or absence of a given genetic polymorphism, we could adjust dosage accordingly. Most genetic polymorphism studied until now have been in genes involved in the metabolism or elimination of drugs. It is thought that these polymorphisms might accelerate or slow drug metabolism or drug elimination.

Ecogenetics is similar to pharmacogenetics, but focuses on the role of genetics in explaining the individual variability of response to environmental factors (carcinogens, pesticides, food products, industrial pollutants, etc.), instead of response to drugs. This information could be used in the workplace to identify individual workers at risk of developing complications related to occupational exposure to specific agents. There is the danger that this might be used to discriminate against those with genetic susceptibility to develop complications, who might be refused employment. On the other hand, workers at low-risk of complications might be exposed to higher levels of the agent in question if it gives them a false sense of security and protective measures are lessened, which

would paradoxically put them at higher risk of actually developing complications.

#### **IV - 7. Personalized Health Care and Genetic Information**

Some hope that a better understanding of genetic variability will help adapt treatments on the basis of an individual's genetic characteristics and the risks and benefits of the many treatment options available for that individual. This will depend on how fast knowledge will grow in pharmacogenetics and ecogenetics. In some cases, the treatment will be the same, but the dose, duration or timing of treatment will be different according to the individual's genotype. In other cases, treatment itself will be tailored for specific individual genotypes, targeting specific genetic differences. Over time, a better understanding of genetic susceptibilities might help target preventive measures to individuals who can potentially benefit from them the most. But, in the context of increasing health care costs, the use of resources to personalize health care based on genetic characteristics will have to be balanced against its benefits.

#### **Conclusion**

The impact of genetics in public health is still limited, but is expected to grow in the near future, as genetic knowledge rapidly increases. Current examples of the use of genetics in public health can serve as lessons for the future.

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*This article should be referenced as such:*

Laberge AM. Genetics and Public Health. *Atlas Genet Cytogenet Oncol Haematol*. 2005; 9(1):86-91.

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